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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,248	07/20/2006	Mimi Adachi	64517.000003	6084

21967 7590 12/22/2008

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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
12/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,248	ADACHI ET AL.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31,34 and 35* is/are pending in the application.

4a) Of the above claim(s) *3,13,14 and 26-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-12, 15-25, 31, 34-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 May 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/9/08;10/24/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-31, 34-35 are pending. The amendment has been entered. Claims 32-33 are canceled. Claims 3, 13-14, 26-30, are withdrawn. Claims 1-2, 4-12, 15-25, 31, 34-35 are under consideration.

Claim Objections

Claim 1 remains objected under 37 CFR 1.75 as being a substantial duplicate of claim 2. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicants have failed to provide as response to said objection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-2, 4-12, 15-25, 31** remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Tamamori-Adachi et al,** [Circ Res, 92:e12-e19, 2003 (IDS)] taken with **Sutterluty et al,** (Nature Cell Biology, 1: 207-214, 1999); **Sherr et al,** [Genes & Development, 13: 1501-1512, 1999, (IDS)]; **Flink et al,** [J Mol Cell Cardiol, 30: 563-578, 1998 (IDS)]; and

Poolman et al, [Circ Res, 85: 117-127, 1999 (IDS)] for the reasons of record in the office action mailed on 1/28/08.

New Claims

Claims **34-35** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tamamori-Adachi et al,** [Circ Res, 92:e12-e19, 2003 (IDS)] taken with **Sutterluty et al,** (Nature Cell Biology, 1: 207-214, 1999); **Sherr et al,** [Genes & Development, 13: 1501-1512, 1999, (IDS)]; **Flink et al,** [J Mol Cell Cardiol, 30: 563-578, 1998 (IDS)]; and **Poolman et al,** [Circ Res, 85: 117-127, 1999 (IDS)] and further in view of **Carrano et al,** [Nature Cell Biology, 1: 193-199, (IDS)].

The teachings of Tamamori-Adachi et al, taken with Sutterluty et al, taken with Sherr et al, taken with Flink et al, taken with Poolman et al, are applied here as mentioned above.

The above combined references teach the importance of co-transfection of adult or neonatal cardiomyocytes with the Ad-D1NLS/Ad-CDK4 and the p45skp2 in order to induce cell cycle progression thus increased cell proliferation compared to control cardiomyocytes. The teachings of Carrano et al supplement the teachings of the combined references by teaching that degradation of the mammalian cyclin-dependent kinase (CDK) inhibitor p27 is required for the cellular transition from quiescence to the proliferative state (abstract). Therefore, the combination of the cited references clearly suggest, that co-transfection of cardiomyocytes with the Ad-D1NLS/Ad-CDK4 and the p45skp2 to cardiomyocytes would induce cell cycle progression at different phases of the cell cycle including the GO phase of the cell cycle when the cells are withdrawn from the cell cycle compared to control cardiomyocytes. Therefore, inherently, the adult cardiomyocytes as taught by the combined cited references provides the method for the proliferating cardiomyocytes that have withdrawn from the cell cycle comprised of Ad-D1NLS/Ad-CDK4 and the p45skp2 in order to induce cell cycle progression.

Tamamori-Adachi/Sutterluty//Sherr/Flink/Poolman/Carrano, taken together, provide teaching, suggestion, and motivation to perform the instantly claimed methods.

The instant claims combine the elements co-transfection of cardiomyocytes with the Ad-D1NLS/Ad-CDK4 and the p45skp2 to cardiomyocytes would induce cell cycle progression at different phases of the cell cycle including the GO phase of the cell cycle when the cells are withdrawn from the cell cycle compared to control cardiomyocytes. This general method has been shown to be used successfully with cardiomyocytes, as expected and predictable function in the instantly claimed methods. Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." KSR International Co. v. Teleflex Inc. (KSR), 550 U.S. at, 82 USPQ2d at 1395.

Therefore, in view of Tamamori-Adachi/Sutterluty//Sherr/Flink/Poolman/Carrano it would be *prima facie* obvious for one of skill in the art to transfect adult cardiomyocyteswith the Ad-D1NLS/Ad-CDK4 and the p45skp2 to cardiomyocytes would induce cell cycle progression at different phases of the cell cycle including the GO phase of the cell cycle when the cells are withdrawn from the cell cycle compared to control cardiomyocytes

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

A. Applicants argue the references alone, or in combination, do not teach introducing a gene encoding a factor that inhibits the production or function of a Cip/kip protein (e.g., of p27kip1) into a cardiomyocyte in vitro. Applicants argue neither Sutterluty nor Sherr directly relates to cardiomyocytes or methods of proliferating cardiomyocytes. Applicants argue Flink relates to cardiomyocytes, but is primarily concerned with the role of retinoblastoma

protein (pRb) in the withdrawal from the cell cycle, and does not teach or suggest introducing a gene encoding a factor that inhibits the production or function of a Cip/Kip protein.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Talmadori-Adachi et al teach the role of cyclin D1 import in cardiomyocyte proliferation by showing that co-infection of recombinant adenoviruses expressing D1NLS and CDK4 sufficiently promoted the re-entry of the cardiomyocytes into the cell cycle. Sherr clearly teaches the mechanism as to why p27kip1 degradation is required fro cells to progress though the cell cycle from late G1 phase into the S phase relatively to cyclin D1, cyclin D1-dependent kinase phopshorylation of Rb and both Cip/kip proteins and Rb and Sherr suggests that p27kip1 degradation is required for cells to progress through the late G1 phase to S phase. Flink by teaching that in differentiated cardiomyocytes p27 is increased, this is sufficient motivation for one of skill in the art of cell cycle regulation to degrade p27 in the cardiomyocytes of Talmadori-Adachi, particularly by the teachings of Poolman where total loss of p27 in the knock out mice resulted in prolonged proliferation of cardiomyocytes (emphasis added). Furthermore, since Sutterly already taught that p27kip is degraded via the ubiqutination molecule p45skp2 it is obvious for a skill in the art of cell cycle regulation to introduce said molecule to degrade p27kip1 in order to progress the cardiomyocytes of the cited references through the cells cycle thus inducing proliferation of the cardiomyocytes. Therefore, the combination of the cited references clearly suggest, that co-transfection of cardiomyocytes with the Ad-D1NLS/Ad-CDK4

and the p45skp2 to cardiomyocytes would induce cell cycle progression thus increased cell proliferation compared to control cardiomyocytes.

Applicants argue that Poolman's disclosure is limited to the developmentall effects of the absence of p27 in neonatal cardiomyocytes. In response, Tamamori-Adachi discloses both neoanatal and adult cardiomyocytes. Therefore, Applicants arguments are not persuasive to the need for specific demonstration of facts and/or reasoning to overcome the rejection because all elements of the method are there.

It is noted that recent KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Ex Parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pt. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Applicant's arguments focus on each reference individually. However, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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Art Unit 1632

/Anne-Marie Falk/
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